Relationship between Radiotherapy and Glycometabolism in Cancer

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Abstract: Cancer cell is able to reprogram its energy metabolism, including aerobic glycolysis, glutamine metabolism, lipid synthesis, and oxidation changes; the abnormal energy metabolism can lead to rapid proliferation, anti-apoptosis, stem cell like features, epithelial mesenchymal transition, metastasis, angiogenesis, immunologic escape, and resistance to radiotherapy and chemotherapy. The Warburg effect is an important expression of reprogramming energy metabolism in cancer and plays an important role in tumor growth, metastasis, and recurrence. Radiotherapy is an important part in combined cancer therapy; 60%–70% of cancer patients need radiotherapy during their entire treatment process. The major mechanism for radiotherapy is believed to kill cancer cells by free radicals induced DNA damage. Aerobic glycolysis in cancer cells is closely related to tumor radiotherapy resistance, and the products of these aerobic glycolysis pathways form a redox buffer network in cancer cells that effectively removes the free radicals and reactive oxygen species, weakening the efficacy of radiotherapy. Therefore, inhibition of glucose metabolism in cancer cells may increase their radio-sensitivity, improve the efficacy of radiotherapy, and improve patient survival.

Key Words: Tumor aerobic glycolysis; Warburg effect; Radiotherapy; Radiation resistance; Cancer

Introduction

Cancer mortality ranks high among chronic diseases in the world, with significant differences between different gender and regions, which shows a continuous growth trend. It is reported that the mortality of cancers in 21st century in China has increased by 83.1%, compared to mid 1970s and increased by 22.5% compared to early 1990s [1]. It is necessary to define the mechanism of the occurrence, development, progression, and metastasis of cancer to improve treatment efficacy, reduce mortality and prolong survival in cancer patients.

Warburg O [2] was the first to propose the aerobic glycolysis of cancer cells, which was based on that mitochondrial function in cancer cells is damaged, the cellular energy is provided by enhancing aerobic glycolysis and no longer through the tricarboxylic acid cycle of mitochondria. This theory gave rise to fierce controversies and has been constantly debated.

In 2011, Hanahan D and Weinberg RA [3] proposed several hallmarks of cancer cells that differ from normal cells; the most important character is the reprogramming energy metabolism of cancer cells. Compared to normal cells, there are aerobic glycolysis and glutamine metabolism disorders, lipid synthesis and oxidation changes in cancer cells, among which the Warburg effect is an important expression of reprogramming energy metabolism in cancer. Further studies support that Warburg effect is widely found in many types of cancers [4,5], and closely related to malignant behaviors such as rapid proliferation, anti-apoptosis, stem cell characteristics, epithelial-mesenchymal transition, metastasis, angiogenesis, immunologic escape, and resistance to radiotherapy and chemotherapy [6-11].

Radiotherapy is one of the major treatments for cancer; it is believed that radiation kills cancer cells by DNA damage-induced free radicals. It is reported that about 60%–70% cancer patients undergo radiotherapy, and the average response rate to radiotherapy is over 40% [12,13]. In this review article, we summarize the advances made recently in investigation of the relationship between glycometabolism and radiotherapy.

Main Pathways and Effects of Glucose Metabolism in Cancer Cells

Main Pathways of Glucose Metabolism in Cancer Cells

Most cells in the body normally obtain sufficient energy through aerobic oxidation, and energy supply by glycolysis only occurs under hypoxia conditions. Glycolysis can supply energy faster but with less output, which is a rapid and effective way to gain energy when the body is in a state of anoxia. However, even under fully aerobic conditions and with intact mitochondrial function, the cancer cells still obtain energy mainly through aerobic glycolysis of glucose, producing lactic acid; the preference for aerobic glycolysis is called Warburg effect [14].

Warburg Effect
Aerobic oxidation of one molecule of glucose can produce up to 32 ATPs, but aerobic glycolysis of one molecule of glucose can only produce two ATPs. However, cancer cells still obtain energy through aerobic glycolysis; this is because ATP produced by aerobic glycolysis is nearly 100 times faster than aerobic oxidation [15], providing a large amount of ATP in a short time to meet the energy demand of cancer cells for rapid proliferation.

It is reported that the cancer cells consume a lot of energy to maintain their physiological needs, resulting in deficiency of their own ATP production and there for aerobic glycolysis is induced for energy supply. When cancer cells consume a large amount of ATP through endoplasmic reticulum enzyme, UDP enzyme ENTPD5, it is necessary to increase energy supply through aerobic glycolysis [16].

Cell proliferation has high demands for nucleotides, amino acids. Cancer cells have unlimited proliferative ability, and aerobic glycolysis is preferred because it converts glucose to lactic acid rather than pyruvate. This energy production process produces aerobic glycolysis intermediates, which can provide substances such as nucleotides, amino acids, and lipids for the biosynthesis of sub-cells after cell division [17].

**Drug Resistance and Radiation Resistance in Cancer Cells**

Several studies have confirmed that cancer cells produce chemical resistance is associated with ATP debt. Compared to normal cells, the ratio of ADP/AMP is decreased and the activity of phosphofructose kinase is increased in drug-resistant cells, indicating that the ATP is consumed at higher rate, so the chemical resistant cells need faster ATP generation to survive, which requires aerobic glycolysis.

Other studies show that, through the Warburg effect, cancer cells accumulate pyruvate, lactate and oxidized reduced glutathione/glutathione disulfide and NAD (P)H/NAD(P) to up-regulate endogenous antioxidant capacity, resulting in resistance to direct and indirect effects of radiation therapy, namely free radicals and oxidative stress caused by radiotherapy [18]. In the meantime, the products of these aerobic glycolysis pathways also form a network of redox buffer in cancer cells, which can effectively remove free radicals and reactive oxygen species and weaken the effects of radiotherapy [19].

**Relationship between Aerobic Glycolysis in Cancer Cells and Radiotherapy**

In the early 1990s, studies revealed that high rate of aerobic glycolysis in primary cancers leads to increase in lactic acid concentration, which has a positive correlation with incidence of metastasis in patients with cervical carcinoma [20] and head and neck cancer [21], indicating that the high aerobic glycolysis turnover rate may be associated with radiation resistance. Meanwhile it is found that monitoring antioxidant glycolysis metabolites such as pyruvate and lactate can predict the radiotherapy response of cancers; this is further strengthened in the study of head and neck squamous cell carcinoma, demonstrating that the concentration of lactic acid after steady state pretreatment is positively correlated with local tumor control after fractionated irradiation [22]. The pretreatment lactate accumulation in primary tumor can produce significant radiation resistance [23]. The data obtained from Quennet V et al. [24] and other studies support that tissue lactic acid content is associated with radiation resistance in solid tumors. Furthermore, the results show that the lactate content measured by noninvasive proton magnetic resonance can be used to predict the radiological resistance of clinical cancers, indicating that transient suppression of aerobic glycolysis during treatment may make the tumor sensitive to radiation.

Taken together, these observations suggest that aerobic glycolysis of cancer cells is closely associated with resistance to radiation [25-29]. If the production of aerobic glycolysis and lactic acid is inhibited, the sensitivity of cancer cells to radiotherapy may increase, thus improving clinical efficacy in cancer patients. It is proven in a previous study that cancer, the conventional segmentation in radiotherapy is more dependent on oxygen than larger segmentation [30]. Leung E et al. [31] have proven that, according to Warburg effect, reducing the lactic acid content and increasing the oxygen consumption in hypoxic cancer can improve the sensitivity to large segmentation radiotherapy and the prognosis of the patients.

Increased expression of Girdin protein [32-34] can promote carcinogenesis, invasion, metastasis, angiogenesis, and autophagy of tumor cells, leading to poor prognosis of cancer patients [35-39]. Yu L et al. [39] have found that decreased expression of Girdin in hepatocellular carcinoma results in decreased glucose absorption and ATP production, indicating that Girdin may regulate energy metabolism in tumorigenesis and cancer development. The data also indicate that the production of lactic acid in liver cancer cells is significantly reduced after decreasing the expression of Girdin, improving the radio sensitivity of liver cancer cells. In addition, Girdin can regulate the aerobic glycolysis of liver cancer cells through the PI3K/AKT/HIF-1α signaling pathway, affecting their sensitivity to radiotherapy.

Several studies have shown that the hypoxia inducible factor-1α (HIF-1α) is an independent predictor of poor prognosis in radiotherapy [40,41], which is considered to be an excellent molecular target for
improving the efficacy of radiotherapy. HIF-1α can regulate the glucose metabolism and cell cycle of cancer cells, increasing the radiation resistance [42-45].

Several methods have been used to inhibit the expression of HIF-1α, including antisense or siRNA [46], Hsp90 inhibitors [47], mTOR inhibitors [48], modulators of microtubule [49] and topoisomerase I [50].

In addition, recent studies have demonstrated that using HIF-1α inhibitor YC-1 to inhibit HIF-1α activity in cancer cells can significantly enhance the effect of radiotherapy [51]. Similarly, the elimination of HIF-1α positive cells in solid tumors by protein drug TOP3 or gene therapy can also increase the sensitivity of cancer cells to radiation [52-54]. It is also found that inhibition of HIF-1α activity in cancer cells at different stages had different effects on radiation sensitivity.

However, it has been reported that, if the activity of HIF-1α is inhibited, cancer cells will resist angiogenesis, increasing radiation resistance [55]. Therefore, future basic research should be done to make sure that the HIF-1α activity is inhibited and then increase the radiotherapy response, produce optimal therapeutic benefits [56].

**Aerobic Glycolytic Enzymes**

The aerobic glycolysis of glucose includes multiple enzymatic steps. It is regulated by more than 10 catalytic enzymes to produce a series of intermediates, as illustrated in Figure 1.

![Image](Image 58x229 to 287x369)

**Figure 1** Key enzymes in aerobic glycolysis of glucose

In the following sections, we will mainly discusses several key aerobic glycolytic enzymes from glucose uptake to lactate acid generation. The abnormal expression of these enzymes has been observed in various types of cancers. Inhibitors of these enzymes are constantly explored for targeted treatments of aerobic glycolysis. In the process of aerobic glycolysis, glucose is initially taken up by glucose transporters (GLUT), a rate-limiting step. GLUT1 is overexpressed in cancer cells to maintain high glucose influx across the cell membrane [57]. After entering the cells, glucose is phosphorylated by hexokinase to produce glucose -6-phosphoric acid. The high HK2 activity in the cancer cells not only results in high rate of glucose consumption and energy production in the proliferation of cancer cells, but also provides precursors for the synthesis of nucleotides and lipids, e.g., G6P [58]. The third step of aerobic glycolysis is the conversion of G6P to fructose-6-phosphoric acid, catalyzed by glucose phosphate isomerase, which has many functions in cancer metastasis, hemocyte differentiation, and neuronal survival [59].

The downstream of PGI, 6- phosphoric acid fructose kinase/fructose -1,6- two phosphatase, regulates the formation of fructose -1 from G6P to 6- phosphoric acid fructose kinase (F-1,6-P), and the level of 6- two phosphoric acid can be used to detect the overexpression of 6- phosphofructose kinase in a variety of human cancer cell lines [60]. Pyruvate kinase (PK) is another important aerobic glycolytic enzyme; the phosphate group is transferred from phosphoenolpyruvic acid to ADP to catalyze the production of pyruvate and another ATP molecule. Studies have shown that PK-M2 is upregulated by c-Myc and HIF-1 [61] and overexpressed in cancer cells, which plays an important role in the metabolism of cancers [62]. It is reported that the consumption of PKM2 in mouse models can accelerate the formation of breast tumors, indicating that PKM2 is necessary for the proliferation of tumor cells [63]. Finally, in order to promote the process of aerobic glycolysis, cancer cells can induce pyruvate dehydrogenase kinase inactivating pyruvate dehydrogenase and stop the pyruvate from entering the mitochondrial matrix to form acetylcoenzyme A. Thus, PDK is almost always up-regulated by c-Myc or HIF in tumor tissues. Apart from PDK, cancer cells also use a great deal of lactate dehydrogenase to reduce pyruvate to lactate, thus regenerating the nicotinamide adenine dinucleotides that necessary to maintain aerobic glycolysis flux. LDH enzyme with high M- subunit content is abundant in cancer cells [64].

Studying on aerobic glycolytic enzyme and its inhibitors tends to explore the inhibition of tumor aerobic glycolysis to control the tumor and improve the cure rate; it would be a way of two-pronged approach if they are combined with radiation therapy. It has been found that the combination of 2-deoxyD-glucose and rotenone to inhibit tumor aerobic glycolysis reduces the radiation resistance at clinically related radiation doses and effectively enhances the therapeutic response to highly active hyperactive metabolic (ovarian) tumors [65]. Dichloroacetic acid is a small molecular PDK inhibitor that can penetrate the blood-brain barrier and reverses the Warburg effect in cancer cells [66]. It has been proven to have moderate antitumor activity [67-69] and induces apoptosis in glioblastoma patients by restoring mitochondrial activity. Some studies have also
used it as a radiosensitizer in lung [70], colon [71] and prostate cancer cells [72]. The aerobic glycolysis phenotype is reversed by combining dichloroacetate with radiotherapy. At the same time, research proofs that dichloroacetate independently and appropriately induces proliferation stagnation in G2-M phrase and reduces the mitochondrial reserve capacity, showing its role in radiation therapy of spongioblastoma cells. In addition, the synergistic reaction of chloroacetate and radiotherapy results in the increased level of mitochondrial ROS and the production of γ-H2AX [73].

MiRNAs and Aerobic Glycolysis

It has been found that MiR-21 works in nearly all solid tumors by regulating tumor suppressors and cell differentiation and/or apoptosis related genes to promote oncogenicity [74]. Studies have proved that miR-21 mediates the enhancement of aerobic glycolysis, which plays an important role in acquired radiological resistance of non-small-cell lung cancer; miR-21 stimulates the high expression of glycolytase by activating the overexpression of HIF-1α.

MiR-133b is a cancer inhibitor in many types of malignancies; low levels of miR-133b expression have been shown in colorectal [75], lung [76], and breast [77] cancers showed. However, the effect of Mir-133b in radiosensitivity is still unclear. Liu G et al. [78] have reported significant down-regulation of miR-133b in non-small cell lung cancer cells with radiation resistance. In addition, miR-133b targets PKM2, inhibiting the aerobic glycolysis in lung cancer cells, which is positively correlated with resistance to radiotherapy.

Conclusion

The level of aerobic glycolysis in cancer is highly correlated with radiation resistance. The reversal of the Warburg effect not only enhances the effect of radiation therapy by inducing oxidative stress, but also induces the dual therapeutic advantage of acid produced by oxidative phosphoric acid coupling. With the continuous development of basic and translational research, we will gradually find intervention approaches to down-regulating tumor aerobic glycolysis and applying them to clinical treatment practice to improve the efficacy and safety of radiotherapy in patients with cancer.

Conflict of Interest

The authors declare that they have no competing interests.

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References


49. Rapisarda A, Urchimieg B, Sordet O, Pommier Y, Shoemaker


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